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ORIGINAL REPORT

Randomized Study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group Comparing Quality of Life in Patients With Ovarian Cancer Treated With Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel

Elfriede R. Greimel, Vesna Bjelic-Radisic, Jacobus Pfisterer, Felix Hilpert, Fedor Daghofer, and Andreas du Bois

From the Department of Obstetrics and Gynecology, Medical University Graz, Graz, Austria; Department of Gynecology and Obstetrics, Universitätsklinikum Schleswig-Holstein, Campus Kiel; Department of Gynecology and Gynecologic Oncology, Dr Horst Schmidt Klinik (HSK), Wiesbaden, Germany.

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Address reprint requests to Elfriede R. Greimel, PhD, Department of Obstetrics and Gynecology, University Graz, Auenbruggerplatz 14, 8036 Graz, Austria; e-mail: elfriede.greimel@meduni-graz.at.

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ABSTRACT

Purpose
The objective of this study was to compare the quality of life (QoL) of ovarian cancer patients treated with paclitaxel/carboplatin (TC) versus paclitaxel/cisplatin (PT) and to determine the impact of treatment toxicity on the various QoL domains.

Patients and Methods
In this phase III trial, 798 patients with ovarian cancer stages IIB-IV were randomly assigned to receive TC or PT. The primary end point was progression-free survival; secondary end points included toxicity, QoL, and response to treatment. Patients completed the European Organisation for Research and Treatment of Cancer QLQ-C30 before treatment, within 3 days before the second and the fourth chemotherapy cycle, and 3 weeks after completion of chemotherapy.

Results
Previously reported data showed that patients undergoing TC or PT did not differ in progression-free survival and overall survival. However, the TC arm was superior, indicating a better overall QoL compared with the PT arm. Controlling for toxicity and age, a significant treatment by assessment time interaction was found for four QoL functioning scales and three symptoms scales. Patients in the TC arm showed better means scores after treatment on overall QoL ($P = .012$), physical functioning ($P = .012$), role functioning ($P = .005$), and cognitive functioning ($P = .024$), compared with the PT arm. Concerning symptom experience, patients undergoing TC showed less nausea and vomiting ($P < .001$), less appetite loss ($P < .001$), and less fatigue ($P = .033$) after completion of treatment compared with patients undergoing PT.

Conclusion
The TC regimen achieved better QoL outcomes compared with the PT regimen. Thus, clinicians may consider replacing cisplatin with carboplatin when treating ovarian cancer patients with chemotherapy.

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INTRODUCTION

Ovarian cancer is the most malignant tumor of the female tract with 192,000 estimated new cases and 114,000 cancer deaths worldwide.[1] Because of inadequate screening tools and a lack of early clinical symptoms, the majority of women are diagnosed with International Federation of Gynecology and Obstetrics stage III or IV disease. Only 20% to 25% of patients are cured, and the majority of patients develop a relapse within the first 5 years after initial diagnosis.[2] Median survival for patients following recurrence is approximately 2 years.[3] Standard treatment for patients with advanced ovarian carcinoma is cytoreductive surgery aiming to remove the visible tumor tissue, followed by combination chemotherapy.[4]

During the past 20 years, the chemotherapy regimens used to treat advanced ovarian cancer have undergone two major advances in efficacy. First, the introduction of platinum-based agents, and second, the introduction of taxanes. Randomized trials showed that carboplatin in combination with cyclophosphamide is better tolerated than cisplatin in combination with cyclophosphamide with no loss of efficacy.[5,6] The first combination of a platinum agent with paclitaxel as first-line therapy in ovarian cancer utilized cisplatin. The paclitaxel/cisplatin (PT) regimen showed better results in terms of progression-free survival and overall survival when

compared with regimens that do not contain taxanes.[7] Caroboplatin, an analog of cisplatin, has less nonhematologic toxicity. The feasibility and tolerability of paclitaxel plus carboplatin (TC) has been tested in several phase I/II studies.[8-10] Two large prospectively randomized noninferiority phase III trials comparing these treatment regimens in terms of toxicity and efficacy showed no significant difference between the two treatment arms concerning survival outcomes.[3,11] However, the TC regimen was better tolerated and had less toxicity than the PT regimen.

Chemotherapy-induced toxicities can have a significant impact on a patient's ability to carry out normal activities of daily living and quality of life (QoL).[12] The major clinical symptom of hematologic toxicity is anemia that severely affects patients' QoL.[13,14] Anemia commonly occurs in cancer patients undergoing myelosuppressive chemotherapy.[15-18] Chemotherapy-induced leucopenia and thrombocytopenia are the most common dose-limited toxicities of myelosuppressive chemotherapy. Adverse gastrointestinal events are also common with paclitaxel but particularly under cisplatin therapy. Nausea and vomiting are the major complaints among cisplatin-treated patients.[19,20] Peripheral neuropathy is one of the principal toxic effects of platinum and taxane chemotherapy, both are standard drugs for ovarian cancer treatment that interfere with self-care activities, physical and role activities, and QoL.[21]

Innovative treatment regimens often do not result in substantial differences in survival. The acceptance of new cancer therapies is sometimes dependent on their QoL consequences. Thus, tolerability of treatment and QoL should be an important focus in research. This article reports on the results of a large clinical trial comparing TC with PT. The primary objective was to determine the treatment efficacy in terms of the proportion of patients without disease progression. Secondary end points included toxicity, response to treatment, and QoL. Previously reported data showed no survival differences among patients treated with TC or PT. However, the TC regimen was associated with a higher frequency of hematologic toxicity but a lower frequency of gastrointestinal and neurologic toxicity compared with the PT regimen.[11]

The objective of the QoL assessment within this trial was to determine the impact of the TC regimen versus the PT regimen on patients' QoL. QoL is a multidimensional concept including physical, emotional, social, and daily-life functioning as well as symptoms related to disease and treatment from the patient's perspective.[22] A preliminary analysis of the QoL data showed that overall QoL was significantly better in the TC regimen than in the PT regimen.[11] As treatment-related adverse effects may negatively impact QoL, we determine the effect of hematologic and nonhematologic toxicity on patients' QoL and symptom experience.

PATIENTS AND METHODS

In this phase III trial, 798 patients with histologically confirmed ovarian cancer stages IIB-IV (International Federation of Gynecology and Obstetrics) were enrolled from 1995 to 1997. Patients who underwent radical debulking surgery were randomly assigned to receive TC or PT. Computer-generated randomization lists were prepared for each study center before the start of the trial using permuted blocks of randomly varying size. Randomization was done by fax to the study office using a registration form. The investigator was informed by fax about the treatment arm.

In the TC arm, paclitaxel (185 mg/m^2) was administered intravenously over 3 hours followed by carboplatin (dose in milligrams = area under the curve × [GFR + 25]) administered intravenously over 30 to 60 minutes. In the PT arm paclitaxel (same dose and schedule) plus cisplatin 75 mg/m^2 was administered intravenously, both given over six courses every 3 weeks. The study was designed in accordance with good clinical practice guidelines, German drug laws, and the Declaration of Helsinki. German and Austrian centers participated in this study, and the local ethics committee of each participating center approved the study. This study was also certified by the German Cancer Society. All patients provided written informed consent before participating in the study.

QoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ-C30) version 2.0. It consists of 30 items comprising five functional scales (physical, role, emotional, social, cognitive), three symptom scales (fatigue, nausea/vomiting, pain), an overall QoL scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The QLQ-C30 has been psychometrically validated cross-culturally. All scales and single items meet the standards for reliability.[23]

QoL assessment was scheduled at baseline (pretreatment), within 3 days before the second and the fourth chemotherapy cycles, 3 weeks after completion of six cycles of chemotherapy (post-treatment), and at every 6 months follow-up. The protocol specified that all centers had an initiation visit including display of all study materials, aim of the study protocol, and detailed information about study administration, including QoL assessment. In each center, a trained nurse or physician was identified to administer the QoL forms. Patients were verbally instructed and assistance was provided in filling out the questionnaire, if needed. QoL assessments were not obtained if patients were too ill and unable to read or write. The compliance with the study procedures was monitored regularly by monitors visiting each center every 2 to 6 months, depending on the number of recruited patients. During these visits, missing QoL forms were regularly discussed and administrators were reminded to improve compliance. The questionnaire completion rate was calculated for patients enrolled in the trial at all assessment points.

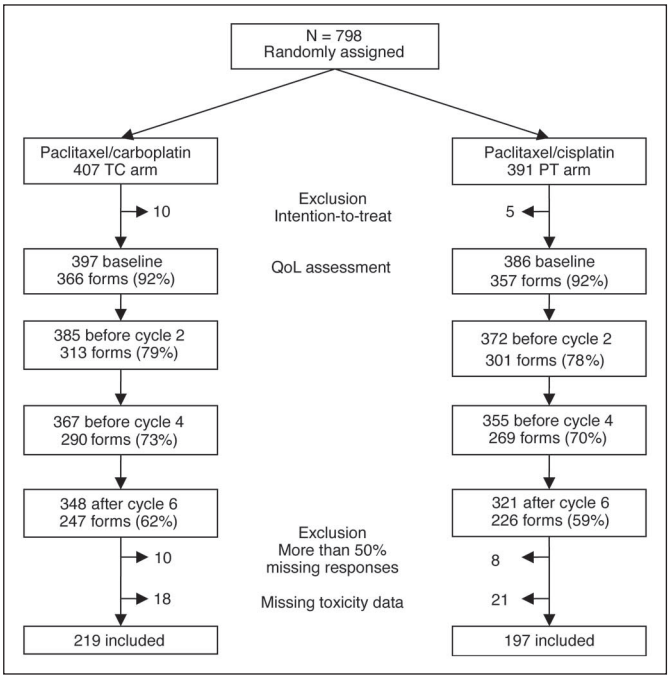

Fig 1. Compliance by study arm for completion of Quality of Life (QoL) questionnaire (QLQ-C30). Percent compliance of trial participants by treatment arm; analyses restricted until cycle 6. TC, paclitaxel/carboplatin; PT, paclitaxel/cisplatin.

Table 1. Differences Between Study Participants and Nonparticipants

Variable	Nonparticipants Mean	Nonparticipants SD	Participants Mean	Participants SD	P
Age, years	58.26	11.25	56.60	10.10	.049
Stratum					.383
FIGO IIb-III with residual tumor > 1 cm					
No.	179		260		
%	54.2		57.4		
FIGO IV with residual tumor > 1 cm					
No.	151		193		
%	45.8		42.6		
Baseline quality of life assessment					
Physical functioning	70.22	28.70	68.73	28.46	.497
Role functioning	56.76	38.66	51.83	38.04	.101
Emotional functioning	59.87	27.99	60.44	27.06	.792
Cognitive functioning	85.08	21.56	85.50	21.23	.798
Social functioning	67.26	34.06	68.40	33.74	.668
Global health status	49.61	24.76	52.45	22.98	.125
Fatigue	45.71	31.46	45.81	29.98	.965
Nausea and vomiting	12.50	23.20	10.12	20.32	.166
Pain	35.37	32.40	34.36	30.83	.680
Dyspnea	22.89	29.67	20.84	29.47	.380
Insomnia	39.21	34.95	36.27	35.63	.287
Appetite loss	35.75	36.67	33.92	36.43	.519
Constipation	27.35	36.48	23.30	34.36	.138
Diarrhea	12.16	24.67	9.81	22.08	.208
Financial difficulties	10.89	25.05	9.68	23.36	.523
Toxicities after 6th cycle chemotherapy					
Hematologic toxicities	0.12	0.43	0.22	0.52	.013
Myalgia/arthralgia	0.15	0.42	0.16	0.45	.630
Gastrointestinal toxicities	0.49	0.80	0.50	0.83	.916
Anemia					.228
Grades 0-1					
No.	155		309		
%	78.7		73.9		
Grade > 1					
No.	42		109		
%	21.3		26.1		
Neurotoxicity					.170
Grades 0-1					
No.	149		289		
%	72.7		67.1		
Grade > 1					
No.	56		142		
%	27.3		32.9		
Survival					
Overall survival, months	48.60	2.22	48.19	1.37	.077
Progression-free survival, months	29.30	1.66	30.91	1.40	.467

NOTE. Survival analyses were carried out by means of the Kaplan-Meier method, using the log-rank test.
Abbreviations: SD, standard deviation; FIGO, International Federation of Gynecology and Obstetrics.

The sample size calculation was based on the primary end point. The trial had sufficient power to detect differences in the QoL scales. The primary and secondary end points were analyzed considering an overall level of $P < .05$. The QLQ-C30 scales and single items were linearly transformed to 0 to 100 and analyzed according to the procedures recommended by the EORTC QoL Group.[24] Higher scores on the functioning scales and the overall QoL scale indicate a higher level of functioning and a better QoL. Higher scores on the symptom scales or single item scales represent a higher level of symptoms or problems.

As suggested by Osoba et al[25] a difference of less than 10 points on a 100-point QoL scale was classified as no change or of small clinical relevance; a difference of 10 to 20 points was considered as moderate; a difference of 20 points or more indicated large effects. For example, an increase of 10 points on a functional scale would mean a moderate improvement, whereas a decrease of 10 points would be interpreted as moderate worsening. Likewise, a rise in a symptom score indicates deterioration; whereas, a reduced score means improvement of the specific symptom. Mean chance scores were calculated as the difference between baseline and post-treatment. A positive mean change score for the functioning scales indicated improvements; whereas, a negative mean change score for the symptom scales indicated worsening.

At baseline, the study sample was compared with reference samples using clinically meaningful differences. Reference data were taken from an international references sample in locally advanced cervical cancer[26] and a normative references sample for a general female population, including 1,139 German women.[27]

For the comparative analysis, differences in the level of QLQ-C30 scores were analyzed by means of a two factorial multivariate analysis of covariance

Table 2. Clinical Characteristics

Variable	TC Arm No.	TC Arm %	PT Arm No.	PT Arm %	P
Age, years					.67
Mean	56.6		57.0		
SD	10.72		9.24		
FIGO stages IIB-III with residual tumor ≤ 1 cm	115	49.6	117	50.4	
FIGO stages IV with residual tumor > 1 cm	104	56.5	80	43.5	.16
Hematologic toxicity, grades 3-4					
Thrombocytopenia	7	3.2	1	0.5	.07
Anemia	2	0.9	5	2.5	.26
Leukopenia	22	10.2	5	2.6	.002
Febrile neutropenia	1	0.5	0	0.0	> .999
Neutropenia	42	23.1	19	10.6	.001
Nonhematologic toxicity, grades 2-4					
Peripheral sensory neuropathy	58	26.5	77	39.1	.06
Central neuropathy	1	0.5	5	2.6	.11
Constipation/ileus	31	14.2	40	20.3	.10
Diarrhea	6	2.7	5	2.5	.90
Mucositis	0	0.0	1	0.5	.47
Stomatitis	2	0.9	2	1.0	> .999
Nausea	22	10.0	55	27.9	< .001
Vomiting	7	3.2	32	16.2	< .001
Myalgia/arthralgia	21	9.6	14	7.1	.36
Pain	17	7.8	15	7.6	> .999
Alopecia	199	90.9	190	96.4	.021
Hypersensitivity/allergy	1	0.5	1	0.5	> .999
Ototoxicity	3	1.4	7	3.6	.20
Dyspnea	20	9.1	11	5.6	.17
Edema	3	1.4	5	2.5	.49
Nephrotoxicity	0	0.0	4	2.1	.048
Cardiac toxicity	4	1.8	5	2.6	.74

Abbreviations: TC, paclitaxel/carboplatin; PT, paclitaxel/cisplatin; SD, standard deviation; FIGO, International Federation of Gynecology and Obstetrics.

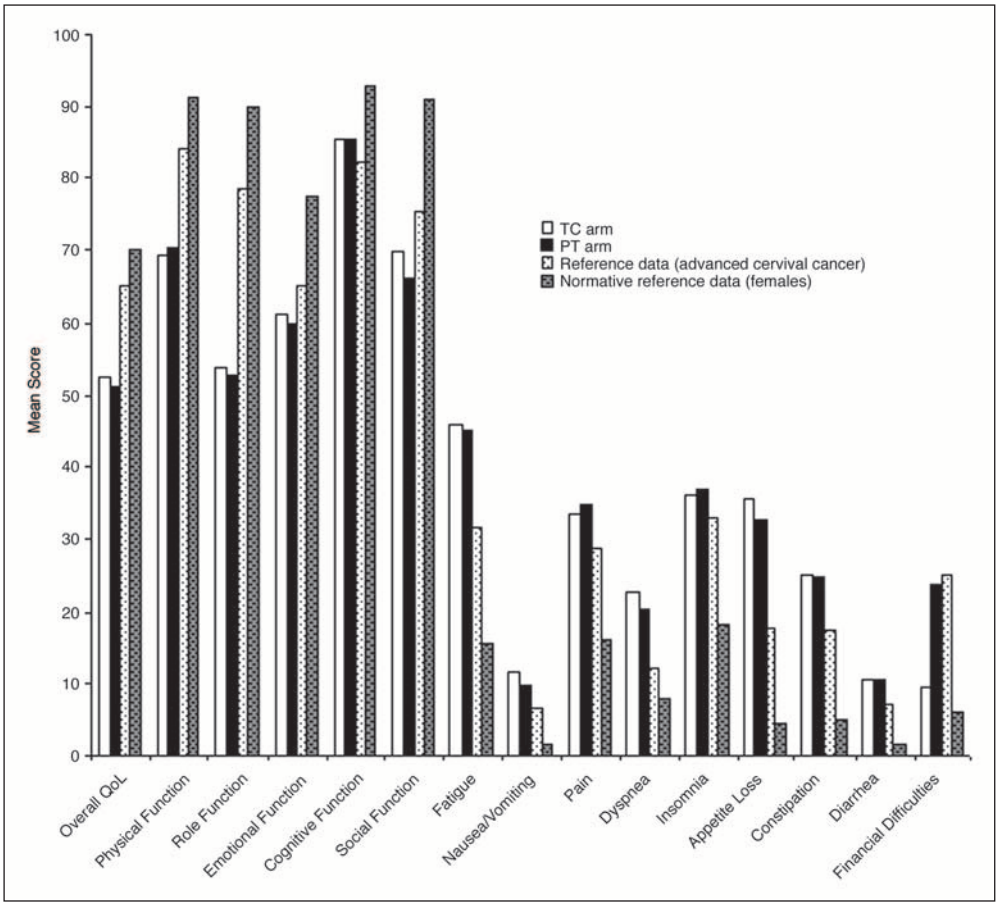

Fig 2. Baseline scores for the Quality of Life Questionnaire (QLQ-C30) by treatment group, advanced cervical cancer reference values and normative reference values. TC, paclitaxel/carboplatin; PT, paclitaxel/cisplatin.

for repeated measures. Hematologic toxicity (thrombocytopenia, anemia, leukopenia, febrile neutropenia, neutropenia), isolated anemia, neurotoxicity (peripheral sensory neuropathy, central neuropathy), gastrointestinal toxicity (constipation, diarrhea, mucositis/stomatitis, nausea, vomiting), and pain (myalgia/artralgia) were used as covariates. Hematologic toxicity was dichotomized in grades 0 to 2 *v* 3 to 4. Nonhematologic toxicity parameters were dichotomized in grades 0 to 1 *v* 2 to 4. Age was also considered as a covariate, since advanced age is a recognized risk factor for the development of chemotherapy-related myelosupression, presumably because of progressive deterioration of renal function with aging and the natural reduction in cellular reserves in the bone marrow.[28]

Multivariate analyses of variance were carried out separately for each assessment time to compare the two treatment arms with respect to the various QoL scales and symptoms scales.

RESULTS

In this trial, a total of 798 patients with ovarian cancer stages IIB-IV undergoing surgery were enrolled and randomly assigned to receive TC combination (n = 407) or PT combination (n = 391). Fifteen of 798 patients were excluded because of violation of inclusion criteria. A total of 397 patients were enrolled in the TC arm, 386 patients were enrolled in the PT arm (Fig 1). Three hundred sixty-six patients in the TC arm and 357 patients in the PT arm provided QoL baseline assessments. QoL compliance rate varied between 92% at baseline and 62% and 59%, respectively, after completion of chemotherapy. Eighteen patients responded to less than half of the questions and 39 patients had missing toxicity data. Patients who were excluded as a result of missing data (mainly because of administration failure to hand out QoL forms) were compared with patients who provided complete QoL data.

The comparison of these two sub-samples in terms of clinical outcomes and QoL baseline scores are shown in Table 1. Study participants were younger compared with nonparticipants (56.6 *v* 58.3 years). There were no statistically significant differences between study participants and nonparticipants in terms of QoL at baseline, stage of disease, and survival. All toxicity parameters were comparable except hematologic toxicity, indicating a lower level of toxicity in patients who were not included in the study.

The statistical analysis was restricted to patients who received six cycles of chemotherapy, had valid toxicity data, and complete QoL data at baseline and post-treatment. Because of the limited response to the QoL questionnaire at the follow-up assessments, no reliable analysis was possible. Treatment arms were well balanced in terms of age and stage of disease. Clinical characteristics and chemotherapy-induced toxicity are presented in Table 2.

Hematologic toxicity (grades 3 to 4) was more frequent in the TC arm except for anemia. The most frequent hematologic treatment side effects were leukopenia and neutropenia, occurring statistically significantly more often in the TC arm ($P < .01$). However, febrile neutropenia occurred only in one patient in the TC arm and did not occur in the PT arm. Thrombocytopenia was found more often in the TC arm. Regarding nonhematologic toxicity (grades 2 to 4), nausea and

vomiting were observed statistically significantly more frequently in the PT arm. Alopecia was the most common symptom in both arms, affecting more than 90% of patients. Peripheral sensory neuropathy and central neuropathy were presented more frequently in the PT arm than in the TC arm. Nephrotoxicity was not presented in the TC arm and rarely in the PT arm. All other nonhematologic toxicity parameters occurred rarely, with no differences in the two treatment arms.

Figure 2 shows the QoL mean scores for the treatment groups at baseline compared with reference values in a clinical sample[26] and in a general sample of 1,139 German women.[27] Ovarian cancer patients in our trial showed lower baseline mean scores in overall QoL, physical functioning, and role functioning and experienced a higher level of fatigue, dyspnoea, and appetite loss than patients with locally advanced cervical cancer. The differences were of moderate clinical importance (10 to 20 points) except for role functioning and appetite loss ($>$ 20 points). Compared with normative reference data in a general female population, ovarian cancer patients in our trial had lower mean scores in all QoL functioning scales (except for cognitive functioning) and higher scores in most symptom scales. These differences were of small or moderate clinical importance.

Comparing pretreatment scores with post-treatment scores, the TC arm was superior, indicating statistically significant improvements in overall QoL, physical functioning, and role functioning and significantly diminished fatigue and appetite loss; whereas, patients in the PT arm showed a significant deterioration in cognitive functioning and increased nausea and vomiting after completion of treatment (Table 3). Concerning clinically relevant changes, an improvement in the TC arm of more than 10 points was found in overall QoL, role functioning, and emotional functioning; whereas, symptoms such as pain and appetite loss diminished by more than 10 points in the TC arm. In the PT arm, the only clinically relevant change from baseline to post-treatment was an increase of nausea and vomiting.

Statistically significant effects were found for the pooled covariate (Mancova), the main effects treatment arm and assessment time, and the interaction treatment arm by assessment time. The results of the pooled covariate analysis including hematologic toxicity, isolated anemia, neurotoxicity, gastrointestinal toxicity, pain (myalgia/arthralgia), and age indicated statistically significant relationships to overall QoL, physical functioning, role functioning, cognitive functioning, and social functioning (Table 4). Hematologic toxicity was not related to any of the QoL domains. When separating anemia from other hematologic toxicity parameters, significant relationships were found for several QoL areas. Anemia was related to lower physical functioning, role functioning, and overall QoL. It also had a statistically significant impact on fatigue. Neurotoxicity (peripheral sensory neuropathy and central neuropathy) was related to impaired physical functioning, emotional functioning, and role functioning. In addition, it had a significant impact on fatigue, pain, insomnia, and financial difficulties. Gastrointestinal toxicity (diarrhea, mucositis, stomatitis, nausea and vomiting) had the most influence on QoL, indicating impaired overall QOL, physical functioning, role functioning, cognitive functioning, and increased symptoms such as fatigue, nausea/vomiting, dyspnea, appetite loss, and constipation. Age as a covariate was associated with impaired overall QoL, physical functioning, and social functioning, significantly more dyspnea, more appetite loss, but less financial difficulties.

Controlling for these covariates, a statistically significant treatment by assessment time interaction was found for four QoL functioning scales and three symptoms scales. Patients in the TC arm showed better overall QoL, physical functioning, role functioning, and cognitive functioning compared with the PT arm after

Table 3. Means and SDs and Mean Change Scores of the EORTC QLQ-C30 Scales by Treatment Arm and Assessment Time

	TC Arm (n = 219)					PT Arm (n = 197)				
	Pretreatment		Post-Treatment			Pretreatment		Post-Treatment		
EORTC QLQ-C30	Mean	SD	Mean	SD	Mean Change Score	Mean	SD	Mean	SD	Mean Change Score
Functioning scales										
Overall QoL/health status	53.3	22.94	63.4	20.49	10.1*	52.0	23.36	55.6	20.77	3.6
Physical functioning	68.0	29.67	77.4	23.40	9.4*	70.2	26.80	71.8	22.24	1.7
Role functioning	52.6	38.16	64.0	29.64	11.3*	52.7	38.11	52.1	30.25	−0.6
Emotional functioning	62.4	27.46	72.7	23.53	10.3	59.2	26.54	64.5	25.86	5.3
Cognitive functioning	85.6	21.24	85.2	21.42	−0.4	85.4	21.60	79.6	24.23	−5.8*
Social functioning	69.6	34.31	74.3	28.87	4.6	68.4	32.96	66.7	31.68	−1.8
Symptoms scales										
Fatigue	46.1	30.47	39.3	27.49	−6.8*	44.1	28.79	44.7	26.99	0.6
Nausea and vomiting	10.6	20.15	9.9	18.51	−0.7	8.3	18.64	23.6	31.22	15.3*
Pain	34.1	30.41	21.5	26.84	−12.6	32.9	30.28	25.0	29.00	−7.9
Single-item scales										
Dyspnea	22.1	29.99	23.3	28.39	1.2	18.8	28.42	23.6	29.59	4.9
Insomnia	36.4	35.85	33.8	32.79	−2.6	34.5	35.21	33.2	34.91	−1.4
Appetite loss	34.6	35.96	12.4	23.78	−22.1*	32.0	35.93	24.8	33.44	−7.2
Constipation	23.1	33.37	14.6	26.51	−8.5	21.5	34.27	19.0	30.52	−2.5
Diarrhea	8.7	20.46	5.9	18.35	−2.7	11.0	23.99	9.2	20.91	−1.8
Financial difficulties	10.2	25.39	15.8	28.57	5.6	9.7	22.12	18.4	29.78	8.6

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire; TC, paclitaxel/carboplatin; PT, paclitaxel/cisplatin; SD, standard deviation; QoL, quality of life.
*Indicates statistically significant differences between treatment arms (Tukey's post-hoc comparison).

Table 4. *P* Values of the EORTC QLQ-C30 Scales by Treatment Arm and Assessment Time Controlling for Age and Hematologic Toxicity

EORTC QLQ-C30	Covariates									
	Hematologic Toxicity	Anemia	Neurotoxicity	Gastrointestinal Toxicity	Myalgia/ Arthralgia Pain	Age	Pooled Covariate	Treatment Arm	Assessment Time	Treatment Arm by Assessment Time
Functioning scales										
Overall QoL/health status	.43	**.014***	.10	**.007***	.17	**.025***	**< .001**	.10	**< .001**	**.012**
Physical functioning	.60	**.012***	**.003***	**.032***	.74	**.001***	**< .001**	.90	**< .001**	**.012**
Role functioning	.40	**.012***	**.008***	**.009***	.25	.85	**< .001**	.25	**.011**	**.005**
Emotional functioning	.70	.11	**.045***	.08	.68	.86	.09	.07	**< .001**	.07
Cognitive functioning	.52	.31	.13	**.021***	.68	.36	**.044**	.34	**.010**	**.024**
Social functioning	.25	.11	.09	.27	.10	**.045**	**.005**	.14	.41	.07
Symptoms scales										
Fatigue	.46	**.001**	**.03**	**< .001**	.58	.13	**< .001**	.65	.07	**.033**
Nausea and vomiting	.57	.91	.59	**< .001**	.61	.88	**< .001**	**.046**	**< .001**	**< .001**
Pain	.14	.07	**.001**	.41	**.006**	.81	**< .001**	.76	**< .001**	.18
Single-item scales										
Dyspnea	.83	.60	.23	**.025**	.86	**.020**	**.032**	.17	.09	.31
Insomnia	.63	.58	**< .001**	.41	.61	.85	**.017**	.23	.33	.76
Appetite loss	.96	.08	.33	**< .001**	.45	**.003**	**< .001**	.37	**< .001**	**< .001**
Constipation	.60	.82	.10	**< .001**	.17	.17	**< .001**	.34	**.003**	.10
Diarrhea	.47	.52	.10	.33	.19	.89	.44	**.037**	.10	.74
Financial difficulties	.89	.57	**.020**	.26	.54	**< .001***	**.001**	.62	**< .001**	.27
Multivariate significance							**< .001**	**.005**	**< .001**	**.001**

NOTE. *P* values < .05 are bolded.
Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire; QoL, quality of life.
*Indicates a negative regression weight.

treatment. Improvements in overall QoL, role functioning, and appetite loss were also clinically relevant. In both arms, cognitive functioning was decreased but more in the PT arm than in the TC arm. Concerning symptom experience, patients in the TC arm showed less nausea and vomiting and less appetite loss and fatigue after completion of treatment compared with patients in the PT arm. Patients treated with PT showed significantly more impairment in cognitive functioning, reported more nausea and vomiting, and reported less change in appetite after completion of chemotherapy compared with patients in the TC arm who had significantly less appetite loss after treatment. In the PT arm, decreased cognitive functioning and increased levels of nausea and vomiting were also clinically relevant. Overall, the negative treatment effects were predominant in the PT arm.

QoL of patients assigned to the two treatment arms were also compared at the two intermediate assessment points using multivariate analyses of variance. Before the second cycle of chemotherapy, patients treated with TC had significantly better overall QoL scores ($P = .046$) and less nausea/vomiting ($P = .002$) but more dyspnea ($P = .004$). These effects were statistically significant but not clinically relevant. Before the fourth chemotherapy cycle, the treatment effects were even stronger, indicating significantly better overall QoL ($P = .006$), emotional functioning ($P = .041$), social functioning ($P = .027$), less nausea/vomiting ($P < .001$), and less appetite loss ($P = .028$) in the TC arm compared with the PT arm. These differences were significant on a statistical level but not on a clinical level.

DISCUSSION

This randomized trial was undertaken to compare two chemotherapy regimens in terms of progression-free and overall survival outcomes as well as toxicity. The results showed that the TC regimen was not statistically significantly different from those of the PT regimen concerning survival outcomes, but the toxicity patterns were different. Hematologic toxicity was significantly more frequent in the TC arm, with neutropenia and leukopenia as the predominant side effects. In the PT arm, nonhematologic toxicity, specifically nausea and vomiting, was observed in more than twice as many patients than in the TC arm. As reported in the original paper, patients receiving TC showed better overall QoL compared with patients receiving PT at any assessment point.[11] At baseline, there were no significant differences between the two treatment arms in any of the QoL scores. We also compared the QoL baseline scores with reference data for patients with locally advanced cervical cancer[26] and with normative reference data for a general population of 1,139 German women.[27] Patients with ovarian cancer participating in this study had lower QoL scores than cervical cancer patients. As expected, the QoL was worse when compared with females of the German reference sample. Ovarian cancer patients had radical surgery within 6 weeks of random assignment. This may have affected patients' QoL at baseline since they may not have been completely recovered from surgery. During treatment, QoL differences between the study sample and the reference samples decreased. After completion of chemotherapy, clinically meaningful differences in QoL diminished for most scales, indicating that women

who have had treatment for ovarian cancer regain QoL function similar to women in the general population.

The QoL of patients was affected differently depending on the chemotherapy combination they received. As previously reported, patients undergoing PT had significantly lower overall QoL scores compared with patients undergoing TC.[11] In our analysis, the same pattern was found for several QoL functioning scales and symptoms scales, indicating better QoL and less symptom experience in the TC group compared with the PT group. Throughout the treatment, the TC regimen was superior to the PT regimen in terms of QoL. These findings are consistent with previous studies, indicating that patients receiving cisplatin had lower overall QoL scores, more appetite disturbance, and nausea and vomiting.[29]

In this study, we included toxicity scores as covariates to find out how much chemotherapy-induced toxicity and which toxicity parameters affect patients' QoL. Hematologic toxicity was statistically significant more frequently in the TC regimen. However, patients treated with TC showed better QoL after treatment compared with patients treated with PT, indicating that these toxicity parameters did not have an adverse impact on QoL. Although neutropenia can be life threatening, in our study its impact on QoL seems to be low. This can be explained by the fact that these side effects are rarely accompanied with clinical symptoms such as febrile neutropenia and infections.

Nonhematologic toxicities, such as nausea and vomiting, were more often reported in the PT arm. These side effects seem to affect patients' QoL to a greater extent than hematologic toxicity. Peripheral neuropathy is the principal toxic effect of chemotherapy for ovarian cancer patients that interferes with self-care activities, mobility, and QoL. This was taken into account in our analysis by dichotomizing neurotoxicity, representing the limit for the impairment of activities of daily living. The most affected domains in our analysis were reduced physical functioning, role functioning, and emotional functioning. Additionally, neurotoxicity had a significant impact on the symptoms scales fatigue and pain. Neurotoxicity is known to persist in some patients for a long time after completion of first-line therapy. This side effect is important with regard to QoL during the treatment-free interval of these patients and during re-introduction of therapy on platinum-sensitive tumors in case of a relapse. Results from a phase III study in the second-line treatment showed that the addition of paclitaxel to platinum improves survival in comparison with platinum without paclitaxel, reinforcing the significance of chemotherapy-induced neurotoxicity and its influence on QoL during the course of disease.[30] Wenzel et al[31] found that one-third of patients undergoing cisplatin and paclitaxel experienced long-term toxicity, such as numbness or tingling. Although, in this study, we were unable to confirm this because of the lack of follow-up data.

A possible limitation of the study is the use of a generic QoL measure without a cancer-specific instrument. Therefore, the effect of specific symptoms that only apply to ovarian cancer patients might have been underestimated. A cancer site–specific measure may have been more sensitive to treatment-related changes; thus, even more effects could have been shown with an ovarian cancer specific instrument. The EORTC ovarian cancer module was under development and, at the time of patient recruitment, not available.

Another limitation of this study is the drop-out rate of patients who did not comply with the planned schedule of QoL assessment or returned incomplete forms. This is a well-known phenomenon that the proportion of patients providing QoL data becomes smaller and smaller in longitudinal studies.[32] To avoid sample bias, we compared study participants with patients who were excluded because of missing QoL forms in terms of the clinical outcomes and QoL baseline scores. Patients who provided QoL assessments did not differ in their baseline characteristics from those who provided QoL data. Surprisingly, hematologic toxicity was significantly lower in the subgroup not responding to subsequent QoL measures. Other toxicity scores were also slightly lower in patients who participated in the study. Furthermore, there were no differences in terms of stage of disease and survival outcomes, which may have been a threat to the validity of our results.

Since carboplatin and cisplatin have equal efficacy in ovarian cancer patients, the results of this study are clinically useful and may assist physicians and patients in the discussion of anticipated treatment effects and their impact on QoL. Given the fact that the TC regimen achieved better QoL outcomes compared with the PT regimen, clinicians may consider replacing cisplatin with carboplatin when treating ovarian cancer patients with chemotherapy.

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Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Jacobus Pfisterer					Bristol-Meyers Squibb (A)	Bristol-Meyers Squibb (B); Bristol-Meyers Squibb (B)		
Andreas du Bois					Bristol-Meyers Squibb (A)	Bristol-Meyers Squibb (B); Bristol-Meyers Squibb (B)		

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Author Contributions

Conception and design: Elfriede R. Greimel, Vesna Bjelic-Radisic, Jacobus Pfisterer, Felix Hilpert, Andreas du Bois
Administrative support: Jacobus Pfisterer, Felix Hilpert, Andreas du Bois
Provision of study materials or patients: Jacobus Pfisterer, Felix Hilpert, Andreas du Bois
Collection and assembly of data: Jacobus Pfisterer, Andreas du Bois
Data analysis and interpretation: Elfriede R. Greimel, Vesna Bjelic-Radisic, Jacobus Pfisterer, Felix Hilpert, Fedor Daghofer, Andreas du Bois
Manuscript writing: Elfriede R. Greimel, Vesna Bjelic-Radisic, Jacobus Pfisterer, Felix Hilpert, Fedor Daghofer, Andreas du Bois
Final approval of manuscript: Elfriede R. Greimel, Vesna Bjelic-Radisic, Jacobus Pfisterer, Felix Hilpert, Fedor Daghofer, Andreas du Bois